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09/912,697	07/25/2001	Nicholas C. Nicolaides	MOR-0040	5193

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EXAMINER

LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 10/20/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/912,697

Applicant(s)

NICOLAIDES ET AL.

Examiner

Zachariah Lucas

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1,3-25 and 27-42 is/are pending in the application.
- 4a) Of the above claim(s) 4-13,28-37 and 39-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,14-25,27,38 and 42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Status of the Claims***

1. Claims 1, 3-25, and 27-42 are pending in the application. Claims 4-13, 28-37, and 39-41 are withdrawn as to non-elected inventions. Claims 1, 3, 14-25, 27, 38, and 42 are under consideration to the extent that they read on the elected invention.
2. In the prior action, mailed on February 25, 2003, claims 1-3, 14-27, and 38 were rejected. In the Response to that action, received by the Office on July 24, 2003, the Applicant cancelled claims 2 and 26, and amended claims 1, 14-25, and 38, and added new claim 42.
3. Because this action raises new grounds of rejection not presented in the prior action, the rejection is made Non-Final.

### ***Claim Objections***

4. **(Prior Objection- Withdrawn)** Claim 26 was objected to in the prior action because of the following informalities: the word "multiantiboitic" is a misspelling of the word "multiantibiotic." The objection is withdrawn in view of the cancellation of this claim.

### ***Claim Rejections - 35 USC § 102***

5. **(Prior Rejection- Withdrawn)** Claims 1-3, 15, and 38 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pre-Grant Publication 2002/0068284 issued to Nicolaides et al. (Nicolaides 1). These claims read on methods of generating antibiotic resistant bacteria by blocking mismatch repair in the bacterium by introducing a dominant negative allele

Art Unit: 1648

of the PMS2-134 mismatch repair gene into the bacterium, contacting the bacterium with at least one antibiotic, selecting bacterium resistant to that antibiotic and culturing the bacterium. The claims have been amended such that the bacteria must now be resistant to multiple antibiotics. Thus, the reference no longer anticipates the identified claims. Further, as the reference does not qualify as prior art under 35 U.S.C. 103(a), no obviousness rejection is being made over this reference.

6. **(Prior Rejection- Withdrawn)** Claim 38 was rejected under 35 U.S.C. 102(b) as being anticipated by the teachings of either of Johnston et al, U.S. patent 6,043,048 or Lin, U.S. Patent 6,025,400. The rejected claim has been amended to read on any bacterium with multiple antibiotic resistance and wherein the bacterium comprises a dominant negative allele of a mismatch repair gene. While at least the Lin reference teaches the existence of bacteria with resistance to multiple antibiotics, the references do not teach such bacteria also comprising the indicated mismatch repair gene. The rejection is therefore withdrawn.

### ***Claim Rejections - 35 USC § 103***

7. **(Prior Rejection- Maintained)** Claims 1-3, 15, 27, and 38 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Nicolaides 1 (U.S. Pre-Grant Publication 2002/0068284). Claim 2 has been cancelled, and claims 1, 15, 27, and 38 have been amended to indicate that the methods result in, and the claimed bacteria comprise, bacteria with resistance to multiple antibiotics and comprising a dominant negative allele of a mismatch repair gene. Claim 42 has been added to application. This new claim reads on the bacteria of claim 38 comprising the dominant negative mismatch repair allele of claim 3. The Applicant argues that

Art Unit: 1648

that the additional limitation of the multiple antibiotic resistance renders the claims non-obvious over the prior art. However, the reference teaches that the hypermutable bacteria used in the application may be used to “screen for novel *mutations* ... that produce variant siblings that exhibit a *new output trait(s)* not found in the wild type cells.” Page 3, paragraph 0029 (emphasis added). Thus, the reference indicates that the bacteria may be used to produce cells with one or with multiple mutations and traits. As the reference also indicates that such traits include antibiotic resistance, it would have been obvious to those in the art to use the method to generate multiple antibiotic resistant bacteria. The rejection is therefore maintained, and extended to new claim 42.

However, it is noted that the Applicant has submitted a paper to the Office indicating that the present invention has been assigned to the same assignee as the Nicolaides I reference. In view of this, the Applicant’s attention is directed to section 706.02(l)(2) of the MPEP. More specifically, MPEP § 706.02(l)(2) II states:

The following statement is sufficient evidence to establish common ownership of, or an obligation for assignment to, the same person(s) or organizations(s):

Applications and references (whether patents, patent applications, patent application publications, etc.) will be considered by the examiner to be owned by, or subject to an obligation of assignment to the same person, at the time the invention was made, if the applicant(s) or an attorney or agent of record makes a statement to the effect that the application and the reference were, at the time the invention was made, owned by, or subject to an obligation of assignment to, the same person.

Thus, such a statement in the present case would avoid the present rejection.

8. **(Prior Rejection- Withdrawn)** Claims 1, 19, 27, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Iris et al., U.S. Patent 6,221,585, in view of Stemmer et al.,

Art Unit: 1648

U.S. PG Pub. 2002/0049104, and Johnston et al., U.S. Patent 6,043,048. The claims have been described in part in the prior action and above. In view of the amendments to the claims, and the accompanying arguments, this rejection is withdrawn.

9. **(Prior Rejection- Reformed and Maintained)** In the prior action, claims 1, 2, 19, 27, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1, 27, and 38 above, and further in view of Aronshtam and Marinus, Nucleic Acids Research, 24(13): 2498-2504. Claims 1, 19, and 38 have been amended as indicated above. Claim 2 has been cancelled from the application, the subject matter of the claim having been incorporated in to claim 1. In view of the amendments, the rejection is restated such that claims 1, 19, 27, and 38 are rejected as obvious over the references identified above, further in view of the teachings of LeClerc (Science 274: 1208-11), Drummond (J Biol Chem, 271: 19645-48), Moreland (Cancer Research, 59:2102-04), and Morris et al. (J Infect Dis 171: 954-60). The teachings of each of these references have been described in the prior action.

The Applicant traverses the rejection by arguing that there is a lack of motivation for those in the art to combine the indicated references, and that the references fail to teach bacteria, and methods of making bacteria, with resistance to a plurality of antibiotics. Because the rejection as reformed comprises elements of other rejections against which traversal were made in the prior action, these other traversals (i.e. the traversals to the rejection of claim 26 and 38) will also be responded to below.

The Applicant's first argument in traversal of this rejection appears to focus on the difference between the teachings of the Iris and Stemmer references. The Applicant argues that

Art Unit: 1648

each of these two references teach a different technique to identify genes associated with a particular phenotype. The Applicant argues that because each of Iris and Stemmer are concerned with different methods of identifying such genes, there is no motivation to combine the references. More particularly, the Applicant argues that because Stemmer is concerned with the evolution of new nucleic acid constructs, there would be no motivation to use such a method of induced evolution in the process of Iris, which teaches hybridization of genes from cells with different phenotypes. The Applicant concludes that the combination of Stemmer and Iris is supported only by impermissible hindsight. The Examiner is not persuaded by this argument.

Stemmer teaches that methods of generating diversity are useful in processes of identifying genes resulting in a phenotypic change. While Iris and Stemmer use different methods to identify genes associated with phenotypes, both of the references are generally concerned with the identification of such genes. Because each of these references is concerned with the common problem of finding methods to identify genetic sources of phenotypic differences, the references are analogous to one another. See, MPEP 2141.01(a) (indicating what is meant by analogous prior art). As indicated in the prior action, Stemmer teaches that inducing genetic variation is useful in such identification, and Iris teaches that it is desirable to identify the genes associated with antibiotic resistance. Further, Stemmer teaches the use of defective mismatch repair mutations to induce phenotypic change. Thus, Stemmer provides a motivation to use such mutations that would be equally applicable to any method of identifying such genetic sources. Because Iris and Stemmer are each concerned with a common problem, and because Stemmer provides a motivation for creating defects in mismatch repair in methods to solve that problem, the combination of these references is not impermissible hindsight as argued by the

Art Unit: 1648

Applicant. Further, as Stemmer teaches that defective mismatch repair can result in increased phenotypic variation, and Aronshtam teaches a dominant negative mutation that results in defective mismatch repair, it would also have been obvious to those in the art to use such mutations to induce the evolution useful in the identification of antibiotic resistance conferring genes. Thus, the Applicant's traversal on the ground of lack of motivation to combine is not found persuasive.

The Applicant's second ground of traversal, as indicated above, is that the added limitation that the bacteria produced are resistant to multiple antibiotics, is not taught or suggested by the combination of Iris, Stemmer, Johnson, and Aronshtam. The Examiner agrees with the conclusion that these references do not, alone, render obvious the amended claims. In view of this, the rejection has been restated to include the references identified in the prior action as rendering original claim 26 obvious. The teachings of LeClerc, Drummond, Moreland and Morris were described in the prior action. As indicated in that action, the first 3 of these references teach that mutations in the mismatch repair genes results in the generation of drug resistance in cells. Morris provides motivation for the generation and study of bacterial cells with resistance to multiple antibiotics. Iris also teaches that the identification of genes associated with antibiotic resistance would be useful for the development of disease control strategies. Abstract; cols 1-2; and col 9, lines 26-31. Thus, from the combined teachings of LeClerc, Drummond, Moreland, Morris and Iris, it would be apparent to those in the art that the use of the method of Iris would also be useful for studying the genes involved with multiple antibiotic resistance, and that such studies would also be useful for the disease control studies.



Art Unit: 1648

It is here noted that the Applicant traversed the rejection of claim 26 in the prior action on the grounds that the identified references do not teach how to generate such multi-antibiotic resistant bacteria, and that the identified references therefore render the claims obvious to try, but not obvious under 35 U.S.C. 103(a). The argument is not found persuasive. It is known in the art that one can generate a colony of resistant bacteria by culturing the cell in an antibiotic containing medium. See e.g., Johnston, col. 2, lines 56-65. From this, it would be obvious to those in the art that multiantibiotic resistant colonies could be generated by culturing the cells in a medium containing two or more antibiotics. Because the method of generating such bacteria is obvious to those in the art, and because the identified references indicate both that mismatch repair deficient cells are likely to develop drug resistance, and because the Morris reference provides a motivation for making such cells, it would have been obvious to those in the art to generate such cells for the same purposes and by the same methods indicated by Iris and Stemmer. The rejection, as reformed, is therefore maintained over the identified claims for the reasons of record, and for the reasons above.

Applicant's traversal of the rejection of claim 38 in the Response (page 16) is also noted. While the traversal was not made in the Applicant's arguments regarding the prior rejection identified above, as the rejection in which the Applicant made the traversal has been withdrawn on other grounds, the argument will be presented here.

The Applicant argued that the "suggestion for working with the genetically stable organisms comes from the teachings of the Applicant." And concludes that the rejection is therefore based on hindsight reconstruction. While the Examiner acknowledges that hindsight reconstruction is an improper basis for rejection, the Examiner does not agree with the

Art Unit: 1648

Applicant's evaluation of the rejection. As was indicated in the prior action, the purpose for one of ordinary skill in the art to make the antibiotic resistant bacteria is so that the gene sequences responsible for the resistance can be identified. In order for such genes to be identified, it would be useful for the cells with the desired phenotypic trait to not undergo further mutation. This is because, where the genome is more stable, those in the art would not have to be so concerned with additional and further mutations of cells being studied, which further mutation may render the process of gene identification more difficult. Because the cells have been rendered hypermutable by the insertion of the dominant negative mismatch repair gene, the unstabilized cells would be likely to generate further mutations that may both make isolation of the resistance conferring mutation more difficult. Thus, one of ordinary skill in the art would be motivated to re-stabilize the cells for study once cells with the desired phenotype had been isolated. Because the motivation and rationale for the re-stabilization limitation is not based on the Applicant's disclosure, but on what one of ordinary skill in the art would reasonable have been expected to know and to do, the rejection is not based on impermissible hindsight, and is therefore maintained.

10. **(Prior Rejection- Withdrawn)** Claims 1, 2, 19, 27, and 38 were rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston in view of Iris and the combined teachings of LeClerc and either Drummond (J Biol Chem, 271: 19645-48, reference AL in the IDS of Dec 31, 2001) or Moreland (reference DO in the same IDS), and further in view of Morris. In view of the amendments to the claims, and the arguments pursuant thereto, the rejection is withdrawn.

Art Unit: 1648

11. **(Prior Rejection- Reformed and Maintained)** Claims 1-3, and 27, 38 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Iris in view of Stemmer and Johnston as applied to claims 1, 2, 27, and 38 above, and further in view of either Nicolaides et al., Molecular and Cellular Biology, 18(3): 1635-1641 (Nicolaides 2) or Nicolaides et al., U.S. Patent 6,146,894 (Nicolaides 3). The status of these claims as amended, and of new claim 42, has been described above. The teachings of the Iris, Stemmer, and Johnston references have also been described above and in the prior action. The Applicant traverses the rejection on the grounds that the identified references do not render obvious bacteria, or a method of making bacteria, comprising a dominant negative allele of a mismatch repair gene, wherein that bacteria is resistant to multiple antibiotics.

The traversal is found persuasive in that the combination of Stemmer, Iris, Johnston, and with of Nicolaides 2 or 3, does not, without further teachings, render obvious the claimed inventions wherein the bacteria are resistant to multiple antibiotics. However, in view of the amendment, the rejection is being reformed as follows: claims 1, 3, 27, 38, and 42 are rejected over Iris in view of Stemmer, Johnston and either or Nicolaides 2 or 3 as applied in the prior action, and further in view of LeClerc, Drummond, Moreland, and Morris as applied in the prior action and as described above. The Applicant's traversal, in the Response, to the use of these references to demonstrate the obviousness of the claimed inventions is noted. As described above, the traversal is not found persuasive. The rejection is therefore maintained against the identified claims.

Art Unit: 1648

12. **(Prior Rejection- Withdrawn)** Claims 1, 14-26, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Iris in view of Stemmer and Johnston as applied to claims 1, 19, and 38 above, or over Johnston in view of Iris and the combined teachings of LeClerc and either Drummond or Moreland as applied to claims 1, 19, and 38 above, further in view of Lin (U.S. Patent 6,025,400, column 1), Chang et al. (U.S. Patent 6,043,220, column 1), Setterstrom et al. (U.S. Patent 6,410,056, column 4), and The Merck Index, (1983, pages 2036, 5032-33, and 6448-449). This rejection is withdrawn in view of the amendments to the claims, the withdrawal of the rejection over Johnston in view of Iris and the combined teachings of LeClerc and either Drummond or Moreland, and in favor of the reformed rejection (above) over Iris in view of Stemmer, Johnston, and Aronshtam.

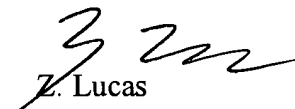
13. **(New Rejection)** Claims 1, 3, 14-25, 27, 38, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of 1) Iris, Stemmer, Johnson, in view of Aronshtam; or 2) Iris, Stemmer, Johnston and either or Nicolaides 2 or 3, and in view of LeClerc, Drummond, Moreland, and Morris and further in view of Lin (U.S. Patent 6,025,400, column 1), Chang et al. (U.S. Patent 6,043,220, column 1), Setterstrom et al. (U.S. Patent 6,410,056, column 4), and The Merck Index, (1983, pages 2036, 5032-33, and 6448-449) as presented in the prior action. As indicated in the prior action, these references demonstrate that the antibiotics identified in the claims were known in the art. It would therefore have been obvious to generate bacteria with resistance to each of these antibiotics for the reasons indicated above with reference to antibiotics generally.


***Conclusion***

14. No claims are allowed.
15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

  
Z. Lucas  
Patent Examiner

  
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